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FORM PTO-1390 (REV. 12-29-99) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: BKY 2 0074

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/857012

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/03999	30 November 1999 (30.11.99)	30 November 1998 (30.11.98)

TITLE OF INVENTION: STENTS FOR BLOOD VESSELS

APPLICANT(S) FOR DO/EO/US: CARO, Colin, Gerald; DOORLY, Denis, Joseph; McLEAN, Mary, Anne

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:
    *Copy of International Publication Number: WO 00/32241
    *Copy of International Search Report

"Express Mail" Mailing Label Number: EL852684191US

Date of Deposit: May 30, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Kathleen A. Nimrichter
(Type or print name of sender)

Kathleen A. Nimrichter
(Signature)

U.S. APPLICATION NO (if known, see 37 CFR 1.5) 09/857012	INTERNATIONAL APPLICATION NO PCT/GB99/03999	ATTORNEY'S DOCKET NUMBER BKY 2 0074

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	CALCULATIONS	PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $690.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	23 - 20 =	3	X $18.00	$ 54.00	
Independent claims	4 - 3 =	1	X $78.00	$ 80.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 994.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 497.00	
SUBTOTAL =				$ 497.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 497.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 497.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ 497.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0308. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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Jay F. Moldovanyi
NAME
29,678
REGISTRATION NUMBER

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Kathleen A. Nimrichter
Kathleen A. Nimrichter

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Colin Gerald Caro et al.
International Application No.	:	PCT/GB99/03999
International Filing Date	:	30 November 1999
For	:	STENTS FOR BLOOD VESSELS
Attorney Docket No.	:	BKY 2 0074

Cleveland, Ohio 44114
May 30, 2001

Assistant Commissioner For Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Prior to examination of the above-captioned patent application, please amend the application as follows:

IN THE ABSTRACT:

Please add the following new abstract:

--ABSTRACT OF THE DISCLOSURE

A stent for supporting part of a blood vessel includes a supporting portion around which or within which part of an intact blood vessel, other than a graft, can be placed so that the stent internally or externally supports that part of the blood vessel. The supporting portion of the stent is of a shape and/or orientation whereby flow within the vessel is caused to follow a non-planar curve. By maintaining a non-planar curvature in the vessel itself, favorable blood flow velocity patterns can be achieved through the generation in the vessel of a swirl flow. Failures in such vessels through diseases such as thrombosis, atherosclerosis, intimal hyperplasia or through blockage, kinking or collapse, can be significantly reduced.--.

IN THE CLAIMS:

Please amend claims 3-7, 9-12, 15, 16, 19-21 and 23 as follows:

3. (Amended) A stent as claimed in claim 1 wherein the supporting portion of the stent is fabricated to incorporate a non-planar curved form.

4. (Amended) A stent as claimed in claim 1 wherein the supporting portion is fabricated to incorporate a geometric arrangement of the vessel whereby the tangent vector from the centreline of the stent intersects the centreline of the vessel by consequence of a symmetric disposition of the stent with respect to the vessel at the junction with the stent.

5. (Amended) A stent as claimed in claim 1 which is of generally hollow tubular shape with three-dimensional curvature.

6. (Amended) A stent as claimed in claim 1 in the form of an open lattice generally tubular framework with discrete openings at each end thereof.

7. (Amended) A stent as claimed in claim 1 comprising a first supporting structure adapted to support or otherwise contact part of the vessel, with a secondary supporting structure extending away from the first supporting structure, but simultaneously capable of supporting the vessel part, said secondary structure capable of maintaining a vessel part when located therein in non-planar curvature.

9. (Amended) A stent as claimed in claim 7 wherein said elongate members define a curved section whose curvature is non-planar.

10. (Amended) A stent as claimed in claim 1 fabricated from a material capable of torsional flexibility, such as from shape memory alloy.

11. (Amended) A stent as claimed in claim 1 which is for use in supporting a vessel part internally, fabricated from a linked mesh or series of linked wire members which is coiled or partly coiled or helical or partly helical.

12. (Amended) A stent as claimed in claim 1 in combination with a device which assists in monitoring the condition of the vessel.

15. (Amended) A stent as claimed in claim 13 wherein the sensor is adapted to transmit signals which can be monitored by at least one of ultrasound, magnetic resonance imaging and electron spin resonance imaging techniques.

16. (Amended) A stent as claimed in claim 13 wherein the sensor portion forms an integral part of the stent and the means of excitation and signal detection are entirely extracorporeal.

19. (Amended) A stent as claimed in claim 17 wherein the sensory device is ring-shaped and is electrically connected to a remote module incorporating power supply, signal detection and recording means.

20. (Amended) A stent as claimed in claim 17 wherein the sensory device is adapted to transmit signals which can be monitored by at least one of ultrasound, magnetic resonance imaging and electron spin resonance techniques.

21. (Amended) A stent as claimed in claim 17 wherein the sensory device forms an integral part of the stent and the

means of excitation and signal detection are entirely extracorporeal.

23. (Amended) A stent as claimed in claim 22 in combination with a sensor device as defined in claim 13.

REMARKS

This application is the entry into the National stage in the United States concerning International Application Serial No. PCT/GB99/03999. That application currently contains a number of multiply dependent claims. Some of those claims are themselves dependent from other multiply dependent claims. As such claim structure is not proper in the United States, applicant takes this opportunity to remove all multiple dependencies from the claims.

Applicant also takes this opportunity to add an abstract to the U.S. application.

Prompt and favorable examination of pending claims 1-23 is respectfully requested.

Respectfully submitted,

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EXHIBIT A

Version with Markings to Show Changes Made

IN THE CLAIMS:

Please amend claims 3-7, 9-12, 15, 16, 19-21 and 23 as follows:

3. (Amended) A stent as claimed in claim 1 [or 2] wherein the supporting portion of the stent is fabricated to incorporate a non-planar curved form.

4. (Amended) A stent as claimed in [any preceding] claim 1 wherein the supporting portion is fabricated to incorporate a geometric arrangement of the vessel whereby the tangent vector from the centreline of the stent intersects the centreline of the vessel by consequence of a symmetric disposition of the stent with respect to the vessel at the junction with the stent.

5. (Amended) A stent as claimed in [any preceding] claim 1 which is of generally hollow tubular shape with three-dimensional curvature.

6. (Amended) A stent as claimed in [any one of claims 1 to 4] claim 1 in the form of an open lattice generally tubular framework with discrete openings at each end thereof.

7. (Amended) A stent as claimed in [any preceding] claim 1 comprising a first supporting structure adapted to support or otherwise contact part of the vessel, with a secondary supporting structure extending away from the first supporting structure, but simultaneously capable of supporting the vessel part, said secondary structure capable of maintaining a vessel part when located therein in non-planar curvature.

9. (Amended) A stent as claimed in claim 7 [or 8] wherein said elongate members define a curved section whose curvature is non-planar.

10. (Amended) A stent as claimed in [any preceding] claim 1 fabricated from a material capable of torsional flexibility, such as from shape memory alloy.

11. (Amended) A stent as claimed in [any preceding] claim 1 which is for use in supporting a vessel part internally, fabricated from a linked mesh or series of linked wire members which is coiled or partly coiled or helical or partly helical.

12. (Amended) A stent as claimed in [any preceding] claim 1 in combination with a device which assists in monitoring the condition of the vessel.

15. (Amended) A stent as claimed in claim 13 [or 14] wherein the sensor is adapted to transmit signals which can be monitored by at least one of ultrasound, [and/or] magnetic resonance imaging [and/or] and electron spin resonance imaging techniques.

16. (Amended) A stent as claimed in [any one of claims 13 to 15] claim 13 wherein the sensor portion forms an integral part of the stent and the means of excitation and signal detection are entirely extracorporeal.

19. (Amended) A stent as claimed in claim 17 [or 18] wherein the sensory device is ring-shaped and is electrically connected to a remote module incorporating power supply, signal detection and recording means.

20. (Amended) A stent as claimed in [any one of claims 17 to 19] claim 17 wherein the sensory device is adapted to transmit signals which can be monitored by at least one of ultrasound, [and/or] magnetic resonance imaging [and/or] and electron spin resonance techniques.

21. (Amended) A stent as claimed in [any one of claims 17 to 20] claim 17 wherein the sensory device forms an integral part of the stent and the means of excitation and signal detection are entirely extracorporeal.

23. (Amended) A stent as claimed in claim 22 in combination with a sensor device as defined in [any of claims 13 to 21] claim 13.

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STENTS FOR BLOOD VESSELS

This invention is concerned with stents for supporting parts of blood vessels. More particularly it is concerned with stents as in-situ supporting devices for arteries and veins within the vascular system. The term 'artery' and 'vein' in the singular or plural, refers to the vein or artery or a part thereof but excludes any parts thereof which is a graft or which has been removed to serve as a graft.

Stents are known devices used in surgery especially in vascular surgery for providing physical support to blood vessels i.e. they can be used to help prevent kinking/occlusion of blood vessels such as veins or arteries and to prevent their collapse after dilatation or other treatment to maintain their patency.

It has been proposed that the flow pattern in arteries including the swirling pattern induced by their non-planar curvature operates to inhibit the development of vascular diseases such as thrombosis, atherosclerosis and intimal hyperplasia.

We have now devised an apparatus and technique for establishing and/or maintaining physiological curvature, including non-planar curvature within blocked, constricted or otherwise flow-restricted blood vessels such as arteries or veins as defined above.

By maintaining physiological curvature, which may

include non-planar curvature in the blood vessels, favourable blood flow velocity patterns can be achieved often through generation therein of 'swirl' flow.

Failures in such vessels through thrombosis, atherosclerosis, intimal hyperplasia or other diseases leading to blockage or due to kinking or collapse, can be significantly reduced.

According to this invention there is provided a stent for supporting part of a blood vessel, such as part of an intact vein or artery within the vasculature, which stent includes a supporting portion around which or within which part of that blood vessel can be placed so that the stent internally or externally supports that part and the supporting portion of the stent is of a shape and/or orientation whereby flow within the vessel is caused to follow a physiologically appropriate curve which may be non-planar.

The supporting portion of the stent may be fabricated to incorporate means to increase the ability of the stent to sustain displacement due to bending and torsion so that it may more readily accommodate

(i) a non-planar curved form; and/or

(ii) it may be pre-formed to provide an appropriate geometry to sustain a more favourable flow in the selected vessel after insertion, and/or

(iii) a geometric arrangement of the junction between the stent and branching vessel e.g. artery whereby

the tangent vector from the centreline of the stent intersects the centreline of the host vessel by consequence of a symmetric disposition of the stent with respect to the host vessel.

The stent may be of generally hollow tubular shape with three dimensional curvature. The stent is particularly preferred for use as an in-situ support internally within or externally around arteries and veins.

The stent may take the form of a series of linked members forming a tubular frame e.g. an open lattice generally tubular framework with discrete openings at each end thereof. Alternatively it may take the form of series of curved rings joined together.

A stent may be passed through the interior section of a blood vessel, which stent then provides support for that part of the blood vessel through which it passes and preferably imparts thereby to the vessel a geometry which includes non-planar curvature i.e. the vessel part supported by the stent can assume and maintain curvature which is non-linear. Part of the supported vessel in such embodiments thereby acquires a geometry which can be regarded as a part-helical or helicoidal curve even if the physical extent of the supported vessel is less than one complete turn of a helix e.g. less than ½ or less than ¼ of such a turn.

A practical embodiment of a non-planar internal stent of type (ii) is one fabricated to adopt an appropriately helicoidal, helical, part helicoidal, or part-

helical form, to provide the required support for the blood vessel after its insertion.

In order that the invention may be illustrated, more easily understood and readily carried into effect by one skilled in this art, reference will now be made to the accompanying drawings of preferred embodiments by way of non-limiting example only, and in which:

Figures 1a to c depict an embodiment of a stent shaped to conform the blood vessel in non-planar curvature at a site where it is deployed,

Figure 2 shows an alternative embodiment of a stent,

Figure 3 shows a configuration of an artery with a stent deployed therein,

Figure 3a is a side view of the Figure 3 arrangement,

Figure 4 shows one suitably shaped stent adapted to establish and maintain non-planar curvature in an arterial part (i.e. part of a whole artery) as shown in Figures 3 and 3a,

Figure 4a is a side view of the Figure 4 stent - supported artery,

Figure 5 is an alternative embodiment of an internal stent based on a clip of e.g. shape memory alloy,

Figures 6a and 6b show a part-helical internal stent,

Figure 6c shows the stent of Figures 6a/6b internally supporting an arterial part,

Figure 7a shows an externally located stent for an artery and a sensor for transmitting flow or other data, and

Figure 7b shows a similar arrangement to figure 7a but wherein the sensor is located within the supported arterial part.

Referring to figures 1a to c of the drawings, the device shown may be fabricated from a thermosettable material, in the form of a hollow tube, the walls of which contain numerous openings so that the interior of the artery is not fully shielded.

In particular, figure 1(a) shows the stent before thermosetting, whereas figure 1(b) and (c) indicate possible configurations whereby prior thermosetting has rendered this stent to adopt the shape of a partially coiled, non-planar curve.

The stent is then inserted within the artery to ensure the geometrical configuration of the artery to a predetermined form in the locality of the stent.

The stent may be of constant diameter, or tapered, as in figure 1(a) to accommodate the common practice of deploying a stent in the vicinity of the junction of the artery with a parent or daughter artery. The stent may be fixed to the artery by sutures (shown arrowed) or to avoid trauma to the vessel, may be attached to a clip ring placed about the vessel.

The restraining action of the stent may be graduated, by mechanically "tapering" the rigidity of the

material: for example, at either end, material may be removed or the rigidity reduced by cuttings. An internally locatable stent is also provided which corresponds to the external stent just described, however such a stent is inserted into the interior of the vessel part rather than being placed exterior to the vessel.

Although intended for the cardiovascular system, embodiments of such stents could be incorporated elsewhere - e.g. in the gastrointestinal system, bile duct, genitourinary system for the "active "stent, this might for example be deployed with treatment of incontinence.

Referring to figure 2 the non-planarity of the vessel 4 is attained by supporting it with an external stent 1, 2 which comprises a longitudinal part section 1 of a cylinder, fabricated of a suitable porous biocompatible material, which may be of straight or curved section, to support that part of the artery 5 in the region of the stent, and integral with part section 1, or attached securely thereto are a plurality of elongate external support members 2, which are fabricated to define an internal region 7 of appropriate non-planar geometry.

The ends 6 of the support members 2 may be secured in situ by surgical thread (not shown) or by a fastening ring 3. The stented vessel 4 is located within that internal region 7.

Figures 3 and 3a depict a non-planar configuration of stent and artery wherein a stent (artery 5, stent 4)

having a non-planar curve is surgically attached offset to the central portion of the artery 5 in that it is at least partly tangential to the artery, see the direction of flow arrow in figure 3a.

The external stent (1,2) of Figure 2 can be modified to support and maintain the non-planar curvature of the artery in the Figure 3/3a arrangements, by for example the structure as depicted in Figures 4/4a. Figures 4 and 4a have reference numerals which correspond with those used in figure 2 described above.

As shown in Figure 5 an internal stent for establishing and/or maintaining non-planar curvature of a vessel part comprises a clip 8 which is part coiled or at least part helical of shape memory alloy, affixed to a cylindrical wire mesh 9. This is an embodiment of a torsionally flexible stent.

Figures 6A and 6B show an alternative embodiment of an internal stent, in which the stent 1 is fabricated from a linked wire mesh of part helical form. The material used is preferably a shape memory alloy to facilitate insertion of the stent. Figure 6C shows the stent located in the vessel post insertion. The stent 4 surgically attached to artery 5 has been shown 'transparent' for purposes of illustration, to show the internally located, part helical wire mesh stent in-situ.

Referring to Figures 7A and 7B, either internal or external stents may incorporate devices which assist in

monitoring the condition of either the graft or the host vessel or both.

In one possible embodiment shown in figure 7A, an external stent 1 incorporates a sensor portion 10 for monitoring the condition of the host artery. The sensor portion is a ring placed over the host artery 5, attached to the tubular stent 1 placed over the graft. The sensor and stent may be secured together by means of clips or threads during the operation to insert the graft. The sensor 10 may incorporate one or several ultrasound probes, or it may comprise a coil for use with magnetic resonance imaging. The sensor portion may be electrically connected by leads 11, only partly shown, to a remote module or modules (not shown) which incorporate the required power supply, signal detection and recording devices for data capture and transmission. Some or all of the modules to which the sensor is connected may be implanted within the body of the person receiving the graft, and incorporate appropriate means such as telemetry for transcutaneous data monitoring.

In a still further embodiment, shown in figure 7B, an external stent 1 comprises a fabric or porous structure 12 attached to several outer supporting members having the external appearance of linked rings or discs 13. For a portion of the stent, these outer members incorporate a sensor device 10a or series of sensors such as miniature radio frequency and/or gradient coils for magnetic resonance imaging, or ultrasound transducers. The power supply for

the sensors, excitation and data monitoring may be as in the figure 7A embodiment. Electrical wires 11 connect the sensor device 10a to the appropriate remote module or modules (not shown).

In another embodiment of an internal or external stent the sensor may incorporate a means to detect certain chemical markers which are indicative of the condition of the flow and/or arteries. It may also contain a means whereby a supply of pharmacological agent may be administered in situ, for example by being connected to an implanted supply of drugs which are caused to be delivered by appropriate implanted machinery.

In other embodiments of an internal or external stent, the sensory action of the stent may derive from the construction of some or all of the supporting members which form the stent. In one such embodiment, the sensory action derives from a coil or coils of an electrically conducting material wound around the perimeter of the stent or interspersed at intervals along the stent which coil or coils may be excited by extracorporeal magnetic and/or electromagnetic fields, and the signal from the stent detected by magnetic coupling with an external detecting coil.

Loss of patency of stents remains a serious problem. The principal pathology at later times is intimal hyperplasia and important sites of its occurrence are apparently immediately upstream and downstream of stents. Most attention appears to have focused on compliance mismatch (arterial distensibility greatly exceeds stent distensibility) as underlying this distribution. However, because stents are effectively straight cylinders and arteries curve three dimensionally, compliance mismatch is also likely to be associated with local distortion of arterial geometry and hence distortion of the flowfield, with implications for vessel biology and pathology.

We propose ex vivo studies of stent-induced distortion of the geometry and flowfield in arteries. Stents will be deployed at a few selected sites of non-planar curvature in physiologically pressurised animal arteries and epoxy resin casts will be made of the stented vessels. Geometric data obtained by MRI from the casts, together with a range of assumed physiological flows, will enable detailed determination of the local flowfield including the distribution of wall shear stress by computational (CFD) simulations. In some instances moulds of the epoxy resin casts will be perfused and the flowfield, measured by MRI, will provide a check on the CFD simulations.

As a step towards remedying the problem of stent-induced distortion of the geometry and flowfield in arteries, we propose the deployment of appropriately pre-shaped stents, obtained by exploiting the shape-memory properties of nitinol. After their deployment the local geometry and flowfield will be studied using the same methods as adopted for control stents. The generation of swirling flows and a reduction of the geometric and flowfield distortion would encourage further deployment of pre-shaped shape-memory stents and/or on the engineering of stents less liable to distort the local geometry and

flowfield.

The principal questions that need to be addressed are:

(1) How is the geometry of an artery which is naturally curved in three dimensions altered by the insertion of a stent, which restricts the ability of the artery to maintain its curvature?

(2) What are the consequences of this modification in the local geometry for the flowfield within the stent and immediately adjacent to it?

(3) What geometric form should a stented portion of artery adopt in order to obtain as uniform a distribution of wall shear stress within the stent and immediately adjacent to the stent as possible?

The local flow pattern in blood vessels (including wall shear) markedly influences their biology and, it appears, the development of vascular disease.

For example, atherosclerosis appears to develop preferentially at locations in arteries where the wall shear is on average low and/or there are large oscillations of wall shear. Furthermore, the preferred region for the occurrence of intimal hyperplasia at end-to-side arterial bypass grafts appears to be where wall shear is low, there is flow separation, and/or there are large oscillations of wall shear during the cardiac cycle. Increase of blood flow (assumed to imply increase of wall shear) decreases the severity of intimal hyperplasia (or causes the regression of pre-existing disease). However, a very large increase of wall shear in small diameter grafts is associated with low patency rates, seemingly because of thrombosis. Several studies suggest that the principal factor determining the flow field is vessel geometry but vessel elasticity and the non-Newtonian nature of blood can affect the details of the flow.

There is an appreciable risk of loss of patency of

stents at later times, principally due to intimal hyperplasia. Stenting is associated with acute mechanical injury to the intima/media. There would not appear to have been detailed work on the role of fluid dynamics in the occurrence of intimal hyperplasia at sites of stenting, or on the preferred sites of occurrence of the process. However, histopathological cross-sections of stented vessels show in some instances a non-axisymmetric distribution of intimal hyperplasia, consistent with a role of the local flowfield in its development.

The Reynolds number for flow in large and medium-sized human arteries is typically much greater than unity, implying that inertial forces dominate over viscous forces. As a result and as implied above, the flowfield is substantially determined by the local geometry. We have recently proposed that the curvature and branching of arteries is commonly non-planar. We have proposed furthermore that the flow is commonly swirling in nature and, unlike that associated with planar curvature and branching, characterised by a relatively uniform distribution of wall shear.

In the light of these proposals and that intimal hyperplasia at end-to-end arterial bypass grafts affects preferentially regions which experience flow wall shear, we have studied the velocity field in model planar and non-planar end-to side grafts, using steady laminar flow and methods including flow visualisation, MRI and computational fluid dynamics. The outstanding findings were much improved mixing within the non-planar model at the 'heel", 'floor' and 'toe,' the preferred sites for intimal hyperplasia. In addition, we found with the non-planar model a marked reduction of peak wall shear stress at the 'floor' of the anastomosis and a greatly increased flux of velocity into the occluded region proximal to the anastomosis. Consequently, wall shear stress in the occluded region was higher with the non-planar model than the planar model.

In recent model studies, we have used a physiological non-steady flow and obtained generally similar results. Moreover, in other recent studies with a model incorporating a sharp bend, we have found non-planar geometry apparently to affect the location and extent of flow separation and markedly to reduce the unsteadiness of the flow.

MR Imaging of Stents In Vitro: Preliminary in vitro MRI studies can be extended, in order to establish the accuracy of imaging the geometry and flowfield in a small series of nitinol stents of different diameter, in the range 8mm-3mm.

The flows will be laminar and either steady or non-steady in the physiological range; it is preferred to use a pump capable of generating physiological flow waveforms. the tubes in which the stents will be deployed will curve in one or more planes. The latter curvature will test the ability to measure stent geometry and the flowfield under nearly physiological conditions.

Although nitinol stents are metallic, their magnetic susceptibility is sufficiently close to that of human tissue to permit high quality MR imaging. Imaging strategies can be investigated which minimise artifacts. These strategies preferably include ultra-short echo times and modified spin-echo methods. Changes to the construction of the stent can also be investigated to create a stent which has both improved flow characteristics and MR imaging characteristics.

MRI Imaging of Stents in Excised Arteries: Nitinol stents supplied in freshly excised pig arteries can be used. Vasomotor activity may be lost in the preparations, but it is unlikely that their distensibility will be grossly abnormal; similar preparations are widely used in vascular distensibility studies.

The stents are preferably deployed for testing at a few selected sites where non-planar geometry can be expected

- probably the origins of the coeliac, renal and common iliac arteries. To ensure near-physiological anatomy and mechanics, the stents can be deployed in vessels still tethered by surrounding tissues and still supported by major structures such as the lumbar spine.

It is possible to prepare vascular casts and study the geometry and flowfield by MRI. Vessel geometry can be determined by preparing epoxy resin casts at physiological transmural pressure; in a few instances casts in different pig preparations will be made at systolic and diastolic pressure, to determine static strain over the pulse pressure. After setting, the cast will be dissected from tissue and imaged in a small-bore MR scanner.

Current designs of stents are shown in Figure 8. A series of rings are provided in which the material has the form of a vase as the ring is harnessed in the azimuthal direction, with occasional link members (see figure 9) which join one ring to the next or simple spot welds.

To incorporate torsional and bending flexibility these link members are replaced by elements with a considerably greater flexibility;

The flexibility may be achieved by increasing the length of the link member whilst changing their point of attachment as in Fig 10.

Alternatively the link members may be made of an appropriate spring like shape.

In the embodiments of figures 10 and 11, the link member is welded at some distance away from closest point, and is more flexible by virtue of increased length.

In the embodiment of figure 12, the link member is a wavy or spring coil form (at least in part) so that it has greater flexibility.

CLAIMS

1. A stent for supporting part of a blood vessel which stent includes a supporting portion around which or within which part of an intact blood vessel other than a graft can be placed so that the stent internally or externally supports that part and the supporting portion of the stent is of a shape and/or orientation which corresponds to the geometry of the vessel whereby flow within the stent-supported such vessel can follow a non-planar curve if present in the vessel at the site of the stent.

2. A stent for an intact blood vessel other than a graft which is adapted to flex three dimensionally but which maintains sufficient torsional flexibility to accommodate and maintain in use non-planar curvature present in arteries or veins.

3. A stent as claimed in claim 1 or 2 wherein the supporting portion of the stent is fabricated to incorporate a non-planar curved form.

4. A stent as claimed in any preceding claim wherein the supporting portion is fabricated to incorporate a geometric arrangement of the vessel whereby the tangent vector from the centreline of the stent intersects the centreline of the vessel by consequence of a symmetric disposition of the stent with respect to the vessel at the junction with the stent.

5. A stent as claimed in any preceding claim which is of generally hollow tubular shape with three-dimensional curvature.

6. A stent as claimed in any one of claims 1 to 4 in the form of an open lattice generally tubular framework with

discrete openings at each end thereof.

7. A stent as claimed in any preceding claim comprising a first supporting structure adapted to support or otherwise contact part of the vessel, with a secondary supporting structure extending away from the first supporting structure, but simultaneously capable of supporting the vessel part, said secondary structure capable of maintaining a vessel part when located therein in non-planar curvature.

8. A stent as claimed in claim 7 wherein the secondary supporting structure comprises a plurality of elongate members linked in the region of their ends remote from the first supporting structure.

9. A stent as claimed in claim 7 or 8 wherein said elongate members define a curved section whose curvature is non-planar.

10. A stent as claimed in any preceding claim fabricated from a material capable of torsional flexibility, such as from shape memory alloy.

11. A stent as claimed in any preceding claim which is for use in supporting a vessel part internally, fabricated from a linked mesh or series of linked wire members which is coiled or partly coiled or helical or partly helical.

12. A stent as claimed in any preceding claim in combination with a device which assists in monitoring the condition of the vessel.

13. A stent as claimed in claim 12 wherein the device is a sensor adapted to transmit a signal responsive to one or more internal flow conditions.

14. A stent as claimed in claim 13 in which the sensor

is ring-shaped and is electrically connected to a remote module incorporating power supply, signal detection and recording means.

15. A stent as claimed in claim 13 or 14 wherein the sensor is adapted to transmit signals which can be monitored by ultrasound and/or magnetic resonance imaging and/or electron spin resonance imaging techniques.

16. A stent as claimed in any one of claims 13 to 15 wherein the sensor portion forms an integral part of the stent and the means of excitation and signal detection are entirely extracorporeal.

17. A stent for supporting part of an intact blood vessel other than a graft which stent includes a supporting portion around which or within which part of that blood vessel can be placed so that the stent internally or externally supports that part, in combination with at least one sensor device adapted to assist monitoring the condition of the vessel.

18. A stent as claimed in claim 17 wherein the sensory device is adapted to transmit a signal responsive to one or more internal flow conditions within the vessel part.

19. A stent as claimed in claim 17 or 18 wherein the sensory device is ring-shaped and is electrically connected to a remote module incorporating power supply, signal detection and recording means.

20. A stent as claimed in any one of claims 17 to 19 wherein the sensory device is adapted to transmit signals which can be monitored by ultrasound and/or magnetic resonance imaging and/or electron spin resonance techniques.

21. A stent as claimed in any one of claims 17 to 20 wherein the sensory device forms an integral part of the stent and the means of excitation and signal detection are entirely extracorporeal.

22. A vascular stent capable of insertion into or attachment externally to an intact blood vessel other than a graft which is adapted to impose non-planar flow therein or adopt its configuration in use to the geometry of the blood vessel so as to maintain therein any blood flow therein which is non-planar.

23. A stent as claimed in claim 22 in combination with a sensor device as defined in any of claims 13 to 21.

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Fig. 1(a)

Fig. 1(b)

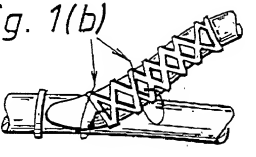


Fig. 1(c)

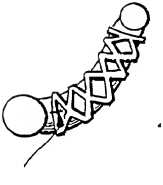
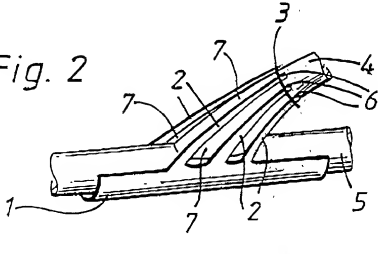


Fig. 2



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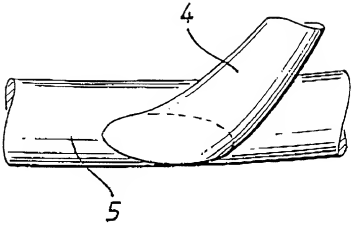
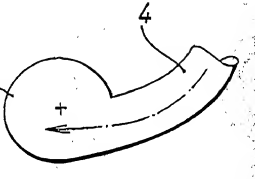


Fig. 3

Fig. 3A



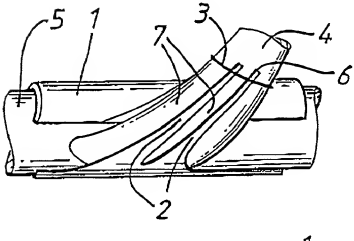


Fig. 4

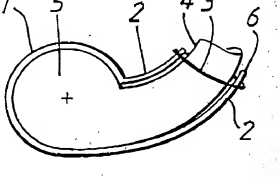


Fig. 4A

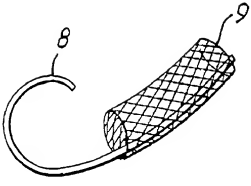
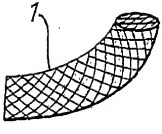


Fig. 5

Fig. 6A



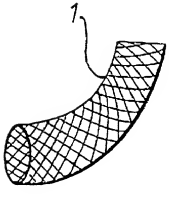


Fig. 6B

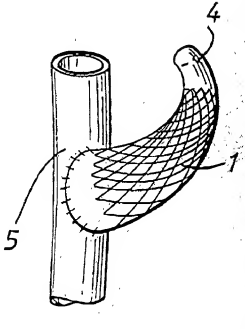


Fig. 6C

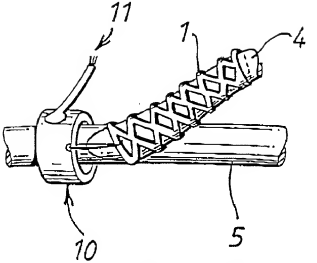


Fig. 7A

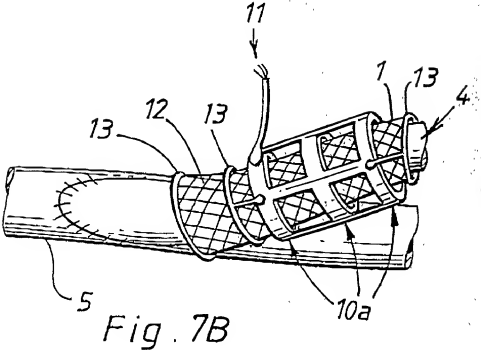


Fig. 7B

Fig. 8

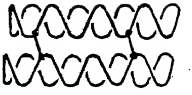


Fig. 9

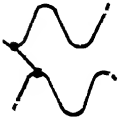


Fig. 10

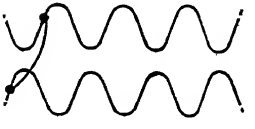


Fig. 11

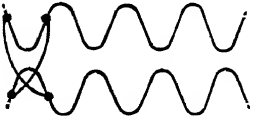
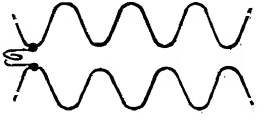


Fig. 12



Attorney Docket No.: BKY 2 0074

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor(if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

STENTS FOR BLOOD VESSELS

the specification of which:

[ ] is attached hereto

[ ] was filed on _____
as Application Serial No. _____
and was amended on _____
(if applicable)

[ ] was filed as PCT/GB99/03999 on November 30, 1999

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed above and have also identified below, by check the box, any foreign application(s) for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application

9826254.6	Great Britain	30 November 1998	
(Number)	(Country)	(Day/Month/Year Filed)	Certified Copy Attached?

I hereby claim the benefit under 35 U.S.C. 119(e) of an United States provisional application(s) listed below.

Application No(s)	(Day/Month/Year Filed)	[ ]additional provisional application numbers are listed on a supplemental priority data sheet attached

I hereby claim the benefit under Title 35, United States, § 120 of any United States application(s) or any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information which is material to patentability as defined in Title 37, of Federal Regulations Code, § 1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(If Applicable)*

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

38

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-00

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